

Study of Solvent Effects by Means of Averaged Solvent Electrostatic Potentials Obtained from Molecular Dynamics Data

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ABSTRACT

We present the theory and implementation of a new approach for studying solvent effects. The electronic structure of the solute, calculated at the *ab initio* level, is obtained in the presence of the surrounding medium. We employ a mean field theory in which the solvent response is described by means of point charges chosen in such a way that they reproduce the average value of the solvent electrostatic potential calculated from molecular dynamics data. In this way, the complete solvent potential can be introduced into the solute Hamiltonian without making use of a one-center multiple expansion of the solute-solvent potential. In the proposed method, only one quantum calculation has to be performed and a great number of configurations can easily be included making the calculation statistically significant. We show that, despite the large fluctuations in the solute charge distribution induced by the solvent, the proposed mean field theory adequately reproduces the energetics and properties of formamide and water molecules in aqueous solution. © 1997 by John Wiley & Sons, Inc.

Introduction

One of the most challenging current problems in theoretical chemistry is the study of molecules immersed in a condensed phase. In systems in which a very reduced number of molecules

intervene (e.g., molecular aggregates or small clusters) or in those characterized by a high degree of symmetry (e.g., crystalline solids), quantum calculations of the whole system may be performed and correlations between the number and nature of the medium molecules and the effects of the medium can be adequately reproduced. However, this approximation is computationally impractical in liquids due to the great number of molecules involved and the absence of symmetry, so that it is

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necessary to employ simpler descriptions of the medium.

Effective Hamiltonian methods¹ (EHM) are especially effective in the study of solvent effects. In these methods, the solute is treated quantum-mechanically while the remaining degrees of freedom of the system, generally assigned to the solvent, are treated classically. The solvent descriptions employed in EHM range from a dielectric continuum² to explicit solvent models³ and include such techniques as integral equations,⁴ simulations,⁵ Langevin dipoles,⁶ etc.

Leaving aside dielectric continuum models that permit one to easily and directly incorporate the solvent effect into the quantum chemistry, but where the microscopic solvation structure in the vicinity of the solute is neglected, the rest of the models may be classified into two types: discrete and averaged. The *discrete* methods select a certain number of solvent configurations, and quantum-mechanical calculations of the solute, including the electrostatic interaction with the solvent molecules, are performed. This approximation has been employed, for instance, by Blair et al.⁵ in a series of reports about solvent effects in electronic transitions, and by Tapia et al.⁷ in a study of solvent effects on the electronic properties of the water molecule. In the second type, one considers an *average* solvent distribution. The electrostatic potential generated by this average distribution is then included in the solute Hamiltonian. Ten-no et al.,⁴ for instance, performed a calculation combining atom-atom radial distribution functions obtained via the extended version of the reference interaction site model with *ab initio* quantum chemistry. A similar approximation was proposed by Sese,⁸ in which the distribution functions were obtained from a molecular dynamics (MD) calculation. In both cases, however, the solute charge distribution was represented through atomic net charges; i.e., only monopole-monopole terms were included in the solute-solvent interaction energy term.

In what follows, we put forward a new method that goes beyond a monopole-monopole approximation. In our method the average electrostatic potential generated by the solvent in the volume occupied by the solute is obtained from simulation data. Then, a set of charges that reproduce the *averaged solvent electrostatic potential* (ASEP) is obtained by a fitting procedure similar to the usual calculations of atomic charges from molecular electrostatic potential (MEP) data, but where now both charges and potential are related to the solvent

molecules. The electrostatic potential due to these charges can then be included in the molecular Hamiltonian as a perturbation.

The method has three characteristics. First, only one quantum calculation has to be performed. This permits very detailed descriptions of the solute molecule to be employed. Second, a great number of solvent configurations can easily be included, thereby making the calculation statistically significant. Last, the solute-solvent interaction energy is calculated very accurately because, for a given representation of the solvent molecules (charges, dipoles, etc.), the complete solvent potential is considered without making use of a one-center multipole expansion of the solvent potential.

The rest of this article is organized as follows. In the next section the details and characteristics of the method are described. Special attention is paid to the selection of the potential sampling points, number and coordinates of the charges, and the fitting procedure. Then, the method is applied to the study of the solvent effects on formamide and water molecules. The final section presents our conclusions.

Methods

Effective Hamiltonian methods assume that solute and solvent wave functions are separable and that the total wave function can be written as a Hartree product. The effect of the solvent then enters as a perturbation to the solute Hamiltonian, which acquires the simple form⁹:

$$H = H^0 + \int dr \Omega V(r, X) \quad (1)$$

Here, H^0 is the Hamiltonian of the solute system *in vacuo*, Ω is the solute charge operator $\Omega = -\sum \delta(r - r_i) + \sum Z_{\alpha i} \delta(r - R_{\alpha i})$, and $V(r, X)$ is the electrostatic potential created by the solvent at a fixed nuclear configuration X . In the mean field approach a statistically significant effective Hamiltonian is obtained by statistically averaging eq. (1) over all solvent configurations:

$$H = H^0 + \int dr \Omega V(r) \quad (2)$$

where $V(r)$ is the ASEP, which is a function of temperature.

At this point, there are two problems that we must solve: first, to calculate the ASEP $V(r)$ inside the volume occupied by the solute; and second, to

obtain a representation of this potential that can be easily introduced into quantum calculations. In our method, we calculate, from MD data, the numerical value of the ASEP over a grid of points defined inside the solute volume. As this numerical potential is not suitable for use in quantum calculations, we propose to represent the ASEP by a set of point charges located in the volume occupied by the solvent. The charges are chosen in such a way that they reproduce the numerical values of the ASEP at the grid points.

The implementation of our method is as follows:

1. *Selection of the potential sampling points.* The van der Waals surface of the solute is calculated and a spatial grid, r_i , is defined inside the volume delimited by the surface.
2. *Calculation of the averaged solvent electrostatic potential.* Explicit solvent simulations are performed. For each solvent configuration the electrostatic potential, $V(r_i, X)$, due to the charge distribution of the solvent molecules, is determined at each point of the grid. Next, the value of the ASEP, $V(r_i)$, is obtained by averaging over the solvent configurations.
3. *Selection of the number and coordinates of the charges.* A set of points, denoted by r_j , is chosen in the region occupied by the solvent. The selection is performed with an eye toward reducing the number of charges to a minimum commensurable with a good definition of the ASEP.
4. *Fitting procedure.* Net electric charges, q_j , placed at the points r_j are determined by empirically fitting the calculated ASEP values.
5. *Quantum calculation.* The electronic wave function of the solute is obtained via the following effective Schrödinger equation:

$$\left[H^0 + \int dr \Omega V(r) \right] | \Psi \rangle = E | \Psi \rangle \quad (3)$$

with

$$V(r) = \sum \frac{q_j}{r - r_j} \quad (4)$$

where H^0 is the Hamiltonian of the solute system *in vacuo* and q_j are the fitted charges.

One of the advantages of the method is that the functional form taken by the ASEP is independent

of the representation adopted for the charge distribution of solvent molecules, whether point charges, dipoles, polarizable dipoles, quadrupoles, etc. In all cases the solvent electrostatic potential is described by means of point charges.

The above process can be made self-consistent, and hence it is possible to simultaneously optimize the electronic structure of the solute in solution and the solvent distribution around it. It is enough to introduce the solute charges obtained from the solute wave function in the potential energy function employed in the MD calculation and repeat steps 2–5 until convergence is reached. In this first article, however, no iterative procedure is performed. Rather, we employ an effective potential in the MD and assume that the solute's influence is already incorporated in the calculation of the solvent distributions.

Details of the Method

In this section, we shall describe the calculation procedure in more detail. We have chosen, as a model system, formamide in aqueous solution. This molecule is representative of groups commonly encountered in biological systems and has been an object of attention in recent years.

A MD calculation was carried out with a timestep of 0.5 fs. The van der Waals parameters for the solute–solvent interaction were taken from previous calculations.¹⁰ The water molecules were simulated by the TIP3P model, consisting of point charges ($q_H = 0.417$ and $q_O = -0.834$), Lennard–Jones constants on O, and fixed intramolecular geometry. The charges used on the solute were $q_C = 0.509$, $q_N = -0.879$, $q_H = 0.391$, $q_H = 0.403$, $q_H = 0.150$, and $q_O = -0.574$. The simulation was started by placing the NH_2CHO at the center of a box containing 214 SPC water molecules. The simulation was run for 50,000 timesteps corresponding to 25 ps (10-ps equilibration, 15-ps production) and the solute–solvent coordinates were dumped at every tenth step for further analysis (1500 configurations). These 1500 configurations were then translated and rotated in such a way that all the solvent coordinates refer to a reference system centered on the solute mass center with the axes lying along the principal axes of inertia of the solute. This process is necessary for the grid to be the same for all configurations.

The algorithm CHELP¹¹ was used to fit the point charges to the ASEP. The procedure is based on Lagrange multipliers. This method has shown

its capacity to yield consistently good results in the determination of atomic charges derived from a molecular electrostatic potential. Furthermore, it allows the charges to be determined in a noniterative way. It is not necessary to make an initial guess at the charges as is the case in nonlinear least-square fits. The details of this method can be found elsewhere.¹¹ Here we only stress that we required the total charge to cancel to zero so that the electroneutrality of the liquid is preserved.

To determine the best values for the parameters involved in the method, we performed a number of test calculations. We studied how the selection of potential points (i.e., the definition of the grid) and the coordinates of the charges that represent the solvent potential affect the quality of the fit.

SELECTION OF POTENTIAL SAMPLING POINTS

The region we are interested in is the volume that is just inside the surface defined by the van der Waals radii of the atoms in the solute molecule. In the construction of this surface we have employed the GEPOL¹² program, which defines the cavity in terms of intersecting spheres centered on the solute atoms. The values of the cavity radii are taken as *f*-times the van der Waals radius, and inside the solute cavity a rectangular three-dimensional grid is defined. We investigated the effect of varying the factor *f* and the number of divisions of the grid, *n*. With this aim, 100 solvent configurations were chosen from the 1500 dynamics data set described previously. For each configuration, a set of charges was determined by fitting the calculated electrostatic potential, *V*(*r*, *X*). In this way, 100 charge sets were obtained. As the spread of the potential used is almost 30 kcal/mol, we can study the capacity of the model to reproduce potentials of several intensities.

The best fits were obtained for *f* between 0.5 and 0.7 (see Tables I and II). The reason that increasing the *f*-value further worsens the fit is that the grid points come too close to the solvent molecules. The same conclusion resulted when the charges were fitted to the ASEP values, with the main difference being that the fits were even better than in the previous case (see Table III). Figures 1 and 2 show the difference map of the fitted-charge electrostatic potential minus the ASEP when *f* = 0.7 and *f* = 0.9, respectively. For *f* = 0.7 the fit is good in all the regions considered. When *f* = 0.9, the ASEP values near the solute nucleus and bonds are well represented, but the regions near the

TABLE I.
Mean Values of *E*_{diff} (kcal / mol).

<i>f</i>	<i>n</i> = 8	<i>n</i> = 10	<i>n</i> = 12	<i>n</i> = 15
0.4	—	2.90	0.126	0.161
0.5	0.750	0.072	0.035	0.019
0.7	0.119	0.081	0.056	—
0.9	0.220	0.120	0.119	—

^a One hundred configurations considered. *E*_{diff} is defined as the difference between the solute–solvent interaction obtained from MD data and from the fitted charges. The solute–solvent interaction energy was calculated as *E* = ΣΣ*q_iq_j/r_{ij}*, where *q_i* are the solute charges and *q_j* are either the solvent charges employed in the MD calculation or the fitted charges.

oxygen and hydrogen atoms are not. This behavior is not modified when the number of points of the grid is increased.

As an additional test, in Table IV we have compared the solute–solvent interaction energies obtained by introducing the effect of a specific solvent configuration into the solute Hamiltonian with the results obtained by introducing the fitted charges. The 4-31G basis set was used in the quantum calculations. The best result is obtained with *f* = 0.5. However, the dipoles are best described with *f* = 0.7.

It is well known that, in the calculations of atomic charges from MEP data, the fit improves asymptotically as the distance between the grid points and the molecule increases. In our case the only way to increase the distance between the grid points and the solvent molecules is to reduce the cavity radius. However, a small *f*-value involves not testing the ASEP values in important regions of the solute. From the above results, we can conclude that a compromise between the quality of the fit and the size of the grid is to take an *f*-value of 0.7 which provides a good fit, includes all the regions of interest, and allows the solute–solvent interaction energies and dipole moments to be adequately reproduced.

TABLE II.
Mean value of the 100 rms (in kcal / mol) Obtained by Fitting the Point Charge Model Electrostatic Potential to Solvent Potential Generated by Specific Solvent Configurations.

<i>f</i>	<i>n</i> = 8	<i>n</i> = 10	<i>n</i> = 12	<i>n</i> = 15
0.4	—	0.69	1.12	0.439
0.5	0.69	0.25	0.25	19.45
0.7	0.50	0.69	0.69	—
0.9	1.63	2.0	2.32	—

TABLE III.
 E_{diff} and rms Fits (in kcal / mol) of Point Charge
 Model Electrostatic potential to the ASEP.^a

f	E_{diff}	rms
0.5	0.008	0.075
0.7	0.009	0.182
0.9	0.000	0.539

^a The charges are chosen to fit the averaged potential generated by 100 solvent configurations.

SELECTION OF CHARGE COORDINATES

Two procedures were adopted in this work to place the fitted charges. In the first, the charges were arranged at a selected number of points around the molecule, on spherical shells, a solvent

diameter apart (see Fig. 3). The shells are centered on the solute mass center. In the second, the shells are adapted to the molecular shape of the solute and defined in terms of intersecting spheres centered on the solute atoms. The charges are distributed in the sphere in the following way: a pentakis dodecahedron in each sphere is inscribed. The solid has 60 faces, all of equal area. The surface of the spheres is then correspondingly partitioned into 60 curvilinear triangles, almost equilateral and uniformly distributed.¹² A charge is then assigned to each curvilinear triangle.

Table V shows the quality of the fits, as a function of the number of shells while maintaining constant the number of charges. The best result was obtained when the charges were placed on the surface of two concentric spheres. When more

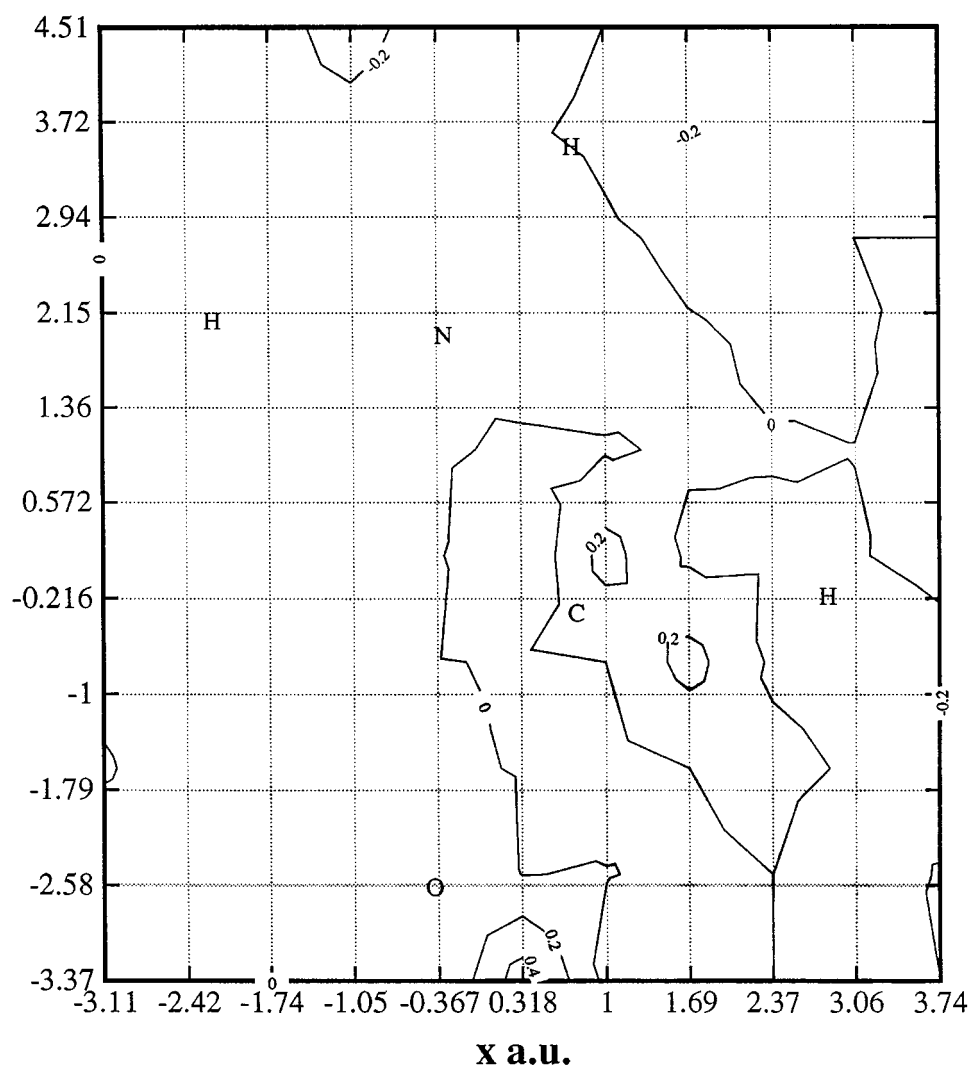


FIGURE 1. Difference map ($y = 0$, $f = 0.7$).

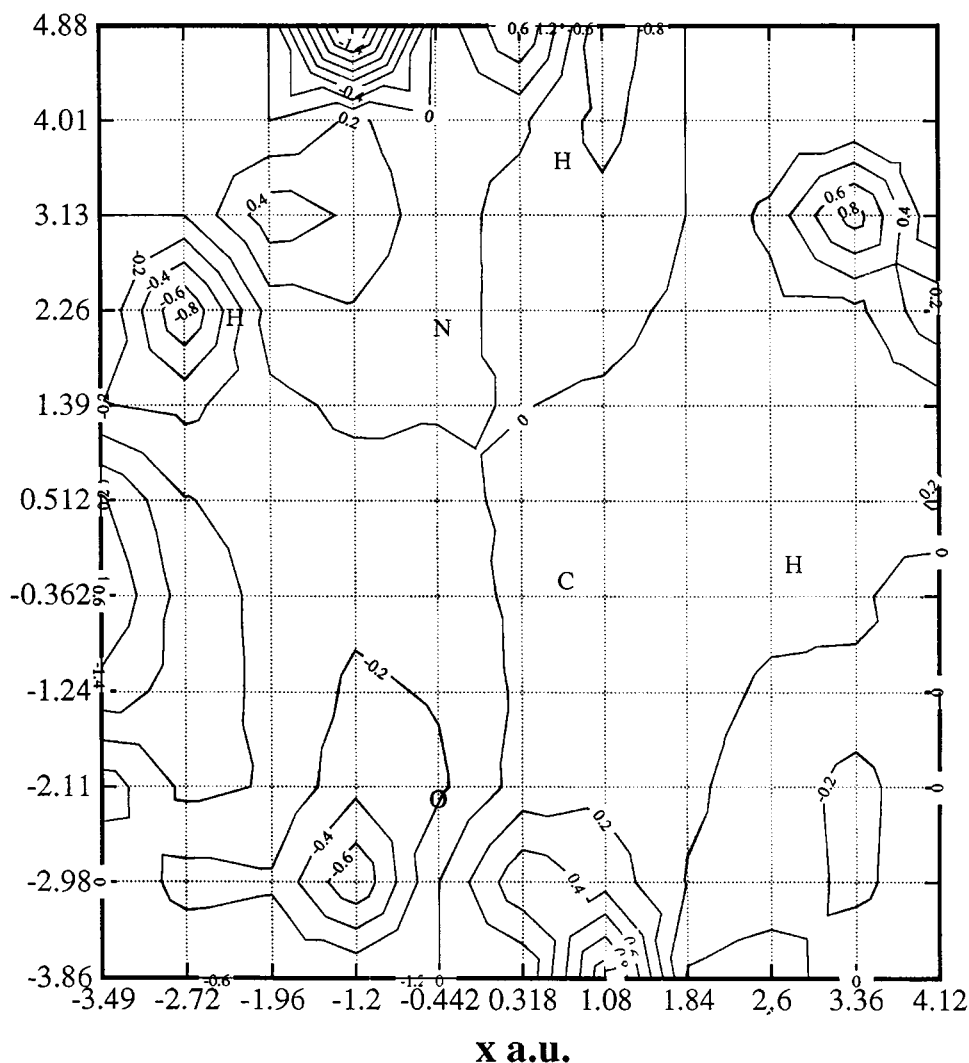


FIGURE 2. Difference map ($y = 0$, $f = 0.9$).

shells were included, the numbers of charges per shell became very small and do not reproduce adequately the ASEP values. Increasing the sphere radius scarcely changed the quality of the fit. Its effect was to increase the magnitude of the charges.

TABLE IV.
 QE_{diff} (kcal/mol) and $Q\mu_{\text{diff}}$ (a.u.).

f	QE_{diff}	$Q\mu_{\text{diff}}$	MaxDiff E	MaxDiff μ
0.5	0.285	0.011	0.434	0.109
0.7	0.323	0.0054	0.627	0.014
0.9	0.355	0.0068	0.627	0.014

QE_{diff} is defined as the difference between the solute-solvent interaction obtained from MD data and from the fitted charges, where the solvent-solvent interaction energy is calculated quantum-mechanically with eqs. (3)–(4). $Q\mu_{\text{diff}}$ is the difference between the dipole moments.

When the solute-shape-adapted surface was employed, the best fit was obtained with only one shell. However, the number of charges required was greater. In conclusion, charges placed on two concentric spheres are sufficient to represent the effect of the solvent electrostatic potential.

Results and Discussion

Having established the validity of our method for reproducing the electrostatic potential generated by specific solvent configurations, we may apply it to the calculation and representation of the ASEP. First, however, we will check that mean field approaches, as given by eq. (2), are suitable for studying solvating effects. The main criticism of averaged theories is that they neglect the correla-

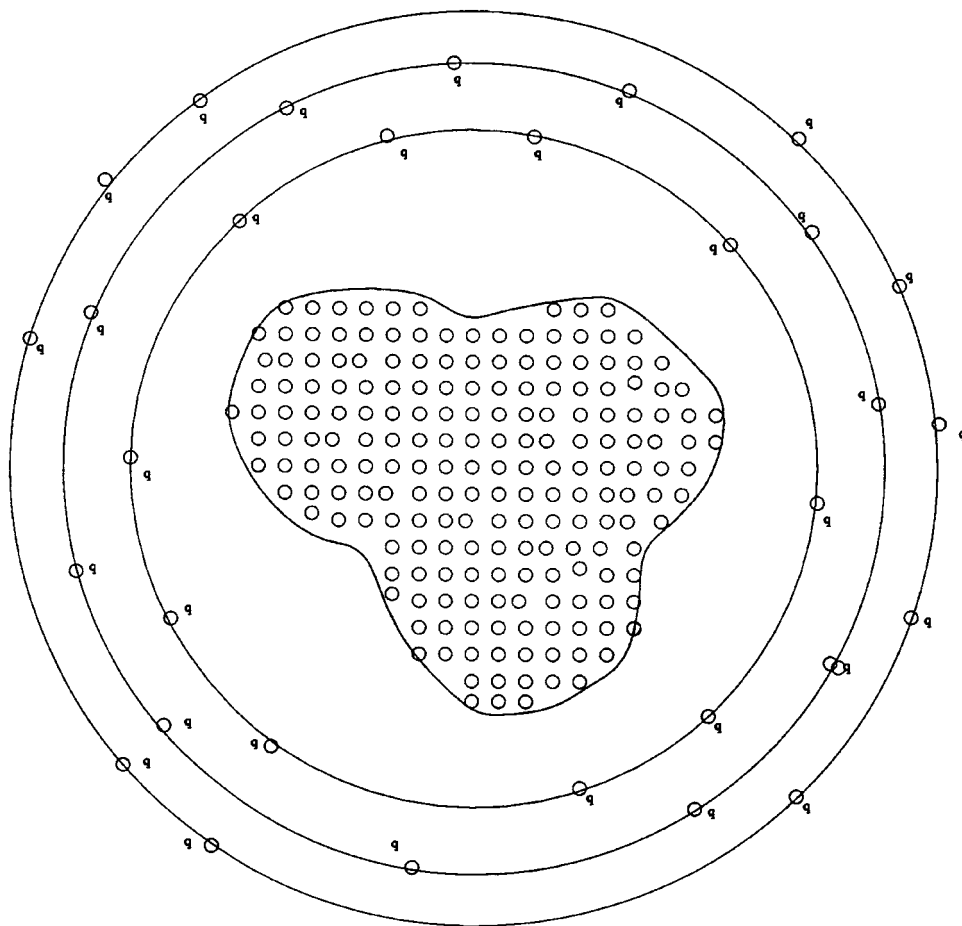


FIGURE 3. Potential sampling points and solvent charges distribution.

tion between the instantaneous solvent configurations and the solute polarization. Let us suppose that the solute charge distribution may be represented as an ideal dipole. In this case, the solute-solvent interaction energy is:

$$W^m = \mu^m E^m = (\mu_0 + \alpha E^m) E^m \quad (5)$$

where E^m is the electric field due to the solvent in the position occupied by the solute and α is

TABLE V.
 E_{diff} (kcal/mol) as a Function of Shell Number.

f	Shell number			Mol. surf. ^a
	1	2	3	
0.5	0.865	0.035	8.641	—
0.7	1.004	0.056	0.099	0.058

^a Solute shape adapted surface. No spheres were assigned to the hydrogen atoms.

the solute electronic polarizability. The averaged solute-solvent interaction energy is obtained by summing over all the configurations:

$$W = \frac{\sum W^m}{N} = \mu_0 \frac{\sum E^m}{N} + \alpha \frac{\sum (E^m)^2}{N} \quad (6)$$

$$W = \mu_0 \langle E \rangle + \alpha \langle E^2 \rangle \quad (7)$$

where the brackets denote averaged values.

In the mean field approach, however, we calculate the energy of an averaged solvent configuration.

$$W_{av} = (\mu_0 + \alpha \langle E \rangle) \langle E \rangle \quad (8)$$

$$W_{av} = \mu_0 \langle E \rangle + \alpha \langle E \rangle^2 \quad (9)$$

The difference between the average energy of the configurations and the energy of the average configuration is then proportional to the solute polariz-

ability and to the fluctuations of the solvent electric field:

$$W_{\text{diff}} = W - W_{av} = \alpha(\langle E^2 \rangle - \langle E \rangle^2). \quad (10)$$

In general, the mean field approach will be valid only if W_{diff} is small with respect to the solute-solvent interaction energy. To determine the validity of this approximation we chose 100 solvent configurations. For each solvent configuration, a quantum-mechanical calculation was performed, which included explicit terms in the formamide electronic Hamiltonian coupling the solvent water atomic positions. Figure 4 shows a histogram of formamide-water interaction energies, ΔE , obtained from the quantum calculation as:

$$\Delta E = E - E^0 \quad (11)$$

where E is the solute energy in the presence of the charges that represent the solvent and E^0 is the *in vacuo* solute energy. In addition to the interaction energy between the solvent and the polarized solute, ΔE includes the variation in the internal energy of the solute as a consequence of its interaction with the solvent, i.e., the energy spent in polarizing the solute. The average value of the 100 solute-solvent interaction energies of the quantum calculation is -24.084 kcal/mol. Next, the ASEP

generated by the same 100 solvent configurations was calculated. The quantum-mechanical calculation employing the charges fitted to the ASEP yielded a value of -23.61 kcal/mol. The difference between the two values is less than 0.5 kcal/mol ($= 2\%$).

In addition to the energy, the dipole moments in solution are very well reproduced. The value obtained for this magnitude when we used the fitted charges is 5.49 D. This compares very well with the average value obtained from the 100 configurations, 5.48 D—a remarkable agreement because large fluctuations in the solute charge distribution are induced by the solvent potential (see the histogram for the module of the total dipole moment depicted in Fig. 5).

Similar results were found in the water-water system. In this case, the average value of the 100 ΔE energies is -26.31 kcal/mol, and the ΔE value provided by the fitted charges was -26.10 kcal/mol. The agreement in the dipole moment was complete—value of 2.96 D was obtained in both cases.

Turning to the formamide-water system, we calculated the ASEP by employing the complete 1500 dynamics data set and obtained one set of charges by the fitting procedure described above. The following parameters were employed: $f = 0.7$, $n = 12$ (with these two parameters there are 600

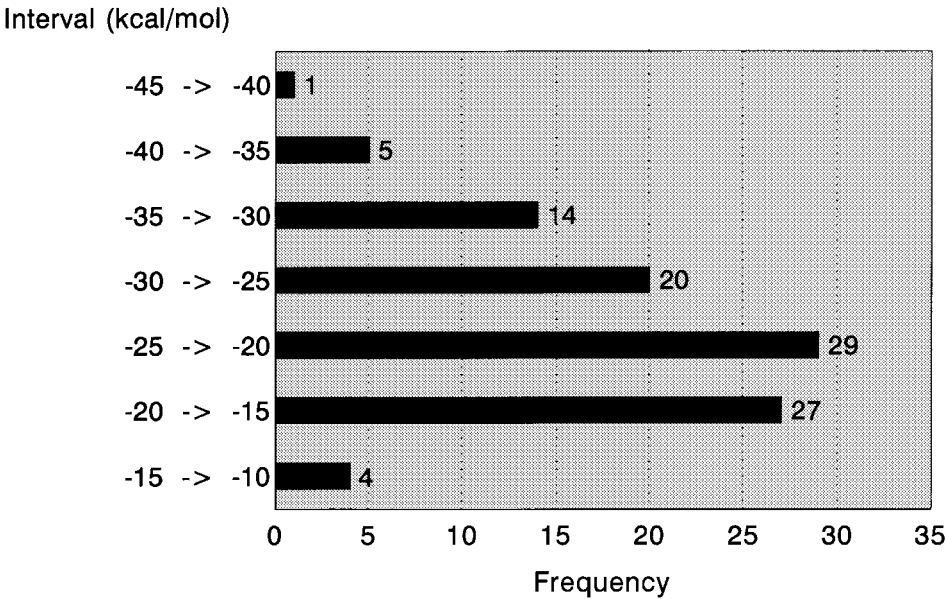


FIGURE 4. Quantum-mechanical solute-solvent interaction energy distribution.

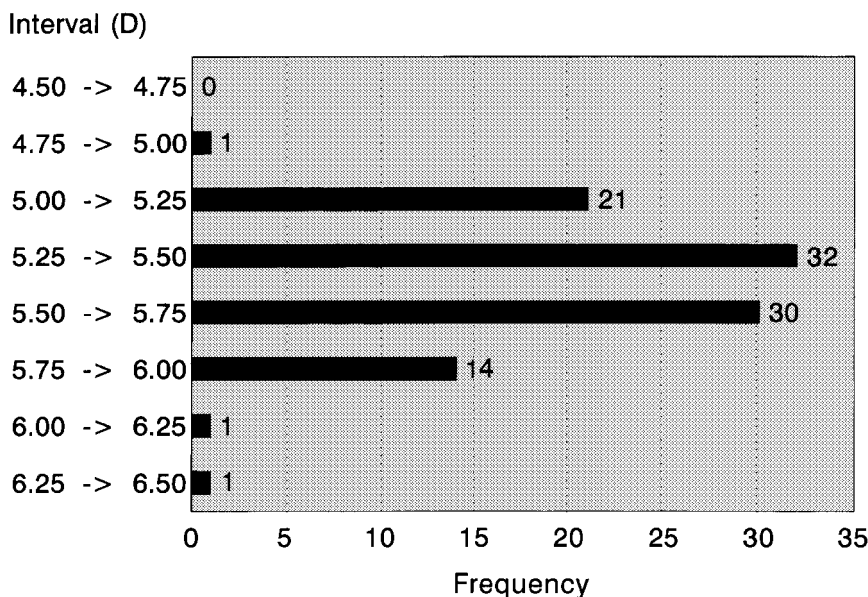


FIGURE 5. Dipole moment distribution for the formamide molecule in water solutions.

grid points). The number of charges was 60, placed in two concentric shells. The rms of the fit was 0.19 kcal/mol. Having obtained the charges, they were introduced into the molecular Hamiltonian, and the effect of the basis set and electronic correlation on the energy, ΔE , and dipole moment, μ , of formamide in solution was analyzed. The results are shown in Table VI.

Three basis sets were studied: 4-31G, DZP, and TZP. These sets yield almost the same dipole moment value and, as a consequence, the solute-solvent interaction energy shows only small variations with basis set. The variation of the dipole moments in solution with respect to the *in vacuo* values is quite notable. The *in vacuo* values range from 4.40 to 4.44 D depending on the basis set employed. In solution, the range is from 5.44 to 5.56 D, the increase being about 25%. The effect of the solute polarization, eq. (6), on the

solute-solvent interaction energies is somewhat lower. If we suppose the solute to be nonpolarizable, i.e., if the calculations are performed by employing the *in vacuo* wave function, then the solute-solvent interaction energies calculated at SCF level decrease by about 2 kcal/mol. This value represents a percentage of about 10%.

The inclusion of the electron correlation (calculated at MP2 level) decreases the ΔE term by almost 2 kcal/mol. This trend is in accord with the results of previous calculations employing the dielectric continuum model¹³ where an appreciable decrease of the free energy of solvation was obtained for carbonyl compounds. As has already been indicated, the ΔE energy is the sum of two terms: the solute-solvent interaction energy and the polarization energy. In our case, as the MP2 correction is applied only to the energy, the solute charge distribution is not modified and the solute-solvent interaction energy remains fixed. It is the polarization term which is affected by the inclusion of the correlation energy: the calculated MP2 solute internal energies are very different *in vacuo* and in solution.

TABLE VI.
Solute-Solvent Interaction Energies (in kcal/mol) and Dipole Moments (Debyes).

	4-31G	DZP	TZP	TZP (MP2)
E_{int}	23.4	23.9	24.1	22.1
μ^a	4.44	4.40	4.44	—
μ	5.47	5.43	5.55	—

The solute-solvent interaction energies were calculated quantum-mechanically with eqs. (3)–(4).

^a *In vacuo* values.

Conclusions

The aim of this article has been to propose an averaged method for the study of solvent effects that combines quantum chemistry and simulation

techniques. In our method, the average solvent electrostatic potential, obtained from MD data, is represented by a set of point charges chosen in such a way that they fit the solvent potential values acting on the solute. One of the main characteristics of the method is that the functional form of the ASEP is independent of the representation adopted for the solvent charge distribution.

It turns out from our study that, although the solvent induces large fluctuations in the solute charge distributions, averaged theories provide a good representation of solvent effects. The proposed method adequately reproduces the energy and properties in solution of the formamide and water molecules.

The main limitations of the theory are related to the neglect of the solvent polarization and to the supposition that the solute and solvent wave functions are separable, i.e., a Hartree product. Explicit consideration of solvent polarization may require associating a polarizability to each solvent molecule. An extended version of the model that accounts for the solvent polarizability effect will be presented in a later article. The inclusion of the exchange and charge transfer components in the solute-solvent interaction will require the explicit consideration of solvent molecules.

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